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10/524,278	03/15/2005	Hiroshi Sato	3190-074	4130

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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,278	SATO ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-16 and 18-21* is/are pending in the application.

4a) Of the above claim(s) *7-9,11,12,14-16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,10,13 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 20, 2008. Currently, claims 1-2, 5-16, 18-21 are pending. Claims 7-9, 11-12, 14-16, 18 have been withdrawn as drawn to non-elected subject matter.

2. This action is FINAL.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

a. The 102 and 103 rejections have been withdrawn in view of the amendments to the claims to require the drug glucuronidation is 2-amino-5-nitro-4-trifluromethylphenol and the enzyme activity of the UGT1 molecule in drug glucuronidation would be lower than that of a UGT1 molecule without the 1456 mutation.

Priority

4. This application is a 371 of PCT/JP03/01475, filed February 13, 2003 and foreign priority application 2002-235029, filed August 12, 2002.

Drawings

5. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 5-6, 10, 13, 19-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to an assay method for drug metabolizing activity of UGT1 comprising a step of detecting a mutation in exon 5 region of a gene coding for UGT that corresponds to nucleotide position 1456 in UGT1 which encodes an amino acid at potion 486 such that the detection of the mutation determines the level of enzymatic activity would be lower than that of UGT1 without the mutation where in the drug glucuronidation is glucuronidation of 2-amino-5-nitro-4-trifluoromethylphenol..

The claims have been narrowed to human subjects, where the mutation at position 1456 in UGT1 determines that the level of enzymatic activity of the UGT1

molecule is lower than that of a UGT1 molecule without the mutation, and the drug is 2-amino-5-nitro-4-trifluoromethylphenol.

The claims remain broadly drawn to all isoforms.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Kurkela specifically teaches Y486D mutation was shown to reduced the activities of the UGT1A1 and UGT1A6. However, surprisingly, the corresponding mutation in the UGT1A9 doubled the Vmax of scopoletin glucuronidation, where as entacapone glucuronidation rate was decreased (abstract). Thus, there is no predictable nature of the glucuronidation between isoforms or different drugs. Kurkela suggests that the Y to D mutation in UGT1A9 might not be detrimental to enzymatic activity, thereby revealing isoform-specific differences due to extensive protein-protein interactions (page 2444, col. 1). Kurkela analyzes the activities of 1A9/Y483D towards scopoletin and entacapone (see Figure 2). The activity and kinetics results clearly show that in sharp contracts to the previous results with UGTs 1A1 and 1A6, the Y483 mutation increased the activity of UGT1A9, at least as far as scopoletin glucuronidation is concerned (page 2446, col. 1). Simply, the mutation affected the scopoletin and entacapone glucuronidation activities of UGT1A9 in different and opposite ways (page 2446, col. 2). Thus, it is clear that there is no predictability between isoforms and different drugs.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002)

teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification.

The specification teaches uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases, UGT) are enzymes that catalyze glucuronidation of various drugs (page 1). The specification teaches that the different UGT enzymes conjugate different substrates (page 1-2). The specification analyzes 2-amino-5-nitro-4-trifluoromethylphenol glucuronide which is glucuronidated by UGT. The specification states that "as long as drugs to be assayed by the invention are glucuronidated by UGT,

they are useful for assay of their metabolism" (page 15, lines 20-26). The specification provides a short list of examples (page 15-16). The specification measured UGT activity with bilirubin and 2-amino-5-nitro-4-trifluoromethylphenol glucuronide as a substrate (page 20). The UGT1A1 molecule UGT gene mutation Y485D (homozygous) was 8% UGT relative activity (page 20). The UGT1A1 molecule UGT gene mutation Y485D (heterozygous) was 36%.

Table 1, page 20, appears to be directed to UGT1A1 molecules with the bilirubin substrate. Page 7, teaches the UGT1A1 mutant has a maximum velocity of about 12% relative to the maximum velocity of the wilt type, and had a Km value which was about half of that of the wild type with respect to 2-amino-5-nitro-4-trifluoromethylphenol. Moreover, Table 2, page 21, appears to be UGT1A6 molecules with 2-amino-5-nitro-4-trifluoromethylphenol as a substrate. The specification does not appear to analyze UGT1A3, UGT1A4, UGT1A5, UGT1A7, UGT1A8 or UGT1A9. Thus, it is unpredictable whether these isoforms would have similarly enzyme activity in response to drug glucuronidation.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims are drawn to glucuronidation of UGT1 isoforms by detecting a mutation at position 1456 in UGT1A1 which encodes an amino acid at position 486 of UGT1A1. The claims remain drawn to detecting a mutation at nucleotide 1456 in the genetic sequence of UGT1 which encodes an amino acid at position 486 of UGT1A1 to deterring the level of enzymatic activity of the UGT1 molecule as lower than that of a UGT1 molecule without the mutation in any isoform. The specification analyzed the UGT1A6 and UGT1A1 isoforms and their mutants with respect to -amino-5-nitro-4-trifluoromethylphenol (see page 7-8). The specification indicates there are additional isoforms of UGT1 including UGT1A3, UGT1A4, UGT1A5, UGT1A7, UGT1A8 or UGT1A9. The art illustrates different isoforms have different enzyme levels and are not predictably associated with one another. Kurkela illustrates the different isoforms have different responses. Kurkela compares the 1A9 and the 1A6 isoforms and finds differences in the effect of the Y483D mutation between the two isoforms (see page 2448, col. 2). Kurkela finds that the C-terminal half of both is identical at the level of amino acid sequence, and the differences in effect must have emerged from differences within the N-terminal half. Therefore, Kurkela illustrates the differences in isoforms and the ability to glucuronidate drugs. The skilled artisan would be required to perform further, unpredictable experimentation to determine how the UGT1A9 and the other isoforms encompassed by the claim would be affected. While the skilled artisan could perform the experimentation, the results of the experimentation are unpredictable and undue. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art of associating polymorphisms with particular condition, the broad scope of the claims would not be enabled at the time the invention was made. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response addresses the teachings of Kurkela and concludes that the findings of Kurkela are not inconsistent with the teachings of the present application. The response asserts that Kurkela describes the effect of the Y483D mutation between the 1A9 isoforms and 1A6 isoforms of UGT1. The response admits that Kurkela states that the Tyr to Asp mutation causes different effects on the enzymatic activity in scopoletin glucuronidation between UGT1A9 and UGT1A6. The applicant also correctly notes that Kurkela does not discuss glucuronidation of 2-amino-5-nitro-4-trifluoromethylphenol (see page 8 of response filed

November 20, 2008. This argument has been reviewed but deemed not persuasive. Kurkela provides that the Y486D mutation (as claimed) has different effects on enzymatic activity when exposed to different drugs. While, Kurkela does not specifically analyze 2-amino-5-nitro-4-trifluoromethylphenol, it is unpredictable whether each of the isoforms respond similarly and would show a lower enzymatic activity than a UGT1 molecule without the mutation, as specifically required by the instant claims.

The response then states that "based upon numerous studies on the effect of mutation at different positions in isoforms of UGT1 on enzymatic activity, it has been found that mutation generally decreases the enzymatic activity of UGT1 isoforms." The response then points the examiner's attention to Guillemette. This argument has been reviewed but deemed not persuasive. It does not appear that either the teachings of Kurkela or Guillemette are directed to 2-amino-5-nitro-4-trifluoromethylphenol. Moreover, the teachings of Gulillemette are not directed to the Y486D mutation. Thus, the teachings of Kurkela are more relevant. For the reasons provided above, it is unpredictable which isoforms have a decrease in UGT1 activity in response to a mutation at 486 and 2-amino-5-nitro-4-trifluoromethylphenol drug. During the telephone interview of October 8, 2008, the examiner specifically stated that applicant may wish to consider filing a declaration to show that the other 7 isoforms recited in the claim (namely A3, A4, A5, A7, A8, A9 and A10) have a lower level of enzymatic activity of the UGT1 molecule in 2-amino-5-nitro-4-trifluoromethylphenol glucuronidation with the Y483D mutation when compared to wild-type.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine A Goldberg/
Primary Examiner, Art Unit 1634
February 10, 2009